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Preparation and evaluation of Ketoprofen beads by melt solidification technique

P. K. Kulkarni, Mudit Dixit*, Yerur S Kumar, Ashwini G Kini and Akash Johri

Dept. of Pharmaceutics, J.S.S College of Pharmacy, J.S.S University, S.S Nagar, Mysore, India.

ABSTRACT

Ketoprofen exhibits short half-life, poor compressibility, caking tendency, gastrointestinal irritation & ulcerogenic effect. Hence, it is desirable to formulate into sustained release dosage form. Amongst different techniques, melt solidification technique is the recently developed technique used to produce sustained release dosage form. Ketoprofen beads were prepared by employing melt solidification technique with lower amount of excipient like cetyl alcohol. This technique involved emulsification and solidification of Ketoprofen-cetyl alcohol melt in an aqueous system followed by cooling and stirring. Cetyl alcohol being a wax, has ability to retard the drug release and acts as emulsifier. Hence, this technique was used to retard release of drug from waxy beads. Amount of Cetyl alcohol used was variable. The Ketoprofen beads were evaluated by DSC, FT-IR, XRD and SEM. Micromeritic and dissolution behavior studies were carried out. Beads exhibited decreased crystallinity and improved micromeritic properties. Release kinetics was studied in simulated gastric fluid and simulated intestinal fluid. No interaction was observed between drug and excipient. Beads obtained were spherical in shape and the yield was about 87%. XRD data were analyzed using Multidimensional minimization Programme, X- ray diffractogramms of drug and beads have shown no significant difference in the inter planar distance (d) values. Crystals of drug and beads were found to be of monoclinic. Drug release from the beads was by diffusion and followed first order kinetics. The study suggests that the Ketoprofen bead prepared by melt solidification technique is a novel approach to formulate sustained release dosage form.

Key words: Beads, ketoprofen, crystallinity, sustained release, dissolution.

INTRODUCTION

Ketoprofen (RS)-2-(3-benzoylphenyl) propionic acid is a non - steroidal anti - inflammatory drug used to treat rheumatoid arthritis, osteoorthritis and mild to moderate pain. The gastrointestinal irritation and ulcerogenic effect with short half - life (1.5 to 2 hours) has led to the design of

sustained release formulations of ketoprofen [1] Due to its hydrophobic nature many attempts have been made to develop wax based sustained release formulation [2]. New techniques such as extrusion-spheronization, spherical crystal agglomeration, melt extrusion and melt granulation are being studied as alternative techniques to overcome the limitations of conventional granulation. Earlier Ketoprofen granules were prepared by melting Ketoprofen powder and cooling the melt. The solidified melt, which comprised of blocks of crystalline Ketoprofen, was subsequently crushed into granules. This multistep process is time consuming. Therefore Melt solidification technique has been designed. Melt solidification technique (MST) involves emulsification and solidification of molten drug and excipient in an aqueous system followed by cooling. Cetyl alcohol has been chosen as excipient, Cetyl alcohol being a wax, acts as an emulsifier and release retardant. Ketoprofen forms a low viscosity melt, which due to its low T_g (-26 ^oC) remains in liquid for longer period of time. Solidification of melt can be accelerated by application of shear [3]. On the basis of these properties a single step melt solidification technique (MST) is employed to obtain beads of ketoprofen.

Melt solidification technique is an important process to control the transition from liquid into solid phase to obtain product in an appropriate form for their transport, storage and subsequent use. This should be done by an economical process, employing the smallest and the simplest equipment possible. The transformation of a melt into a solid with a certain appearance and specific physical properties is an important operation in chemical and process industries. In most cases, the solidification is a crystallization without the aim of separation. Crystallization under defined process conditions influence properties of the solidified melt such as shape, size, crystalline structure, hardness and dust content. During the last couple of decades the large variety of different requirements for the final size and shape of a product has led to a considerable number of solidification processes[4].

The aim of the present study was to develop sustained release ketoprofen beads employing the strength of melt solidified and to impart sphericity with minimum amount of excipient. The beads were characterized using scanning electron microscope (SEM), FT – IR, X-ray diffraction, yield, micromeritic properties and various release parameters were evaluated using different medias like simulated intestinal fluid and simulated gastric fluid.

MATERIALS AND METHODS

Ketoprofen was obtained as a gift sample from Micro labs, Bangalore, India. All chemicals and buffers used were of analytical grade.

Table.1 Formulation of Ketoprofen beads with varying concentration of Cetyl-alcohol.

Formulation No	Amount of Ketoprofen	Amount of Cetyl alcohol
F1	250mg	250mg
F2	250mg	500mg
F3	250mg	750mg
F4	250mg	1000mg
F5	250mg	1250mg

Preparation of Ketoprofen beads:

A mixture of Ketoprofen and cetyl alcohol at different ratios (table.1) were melted and stirred on a water bath maintained at 95°C to form a uniform molten mass. The Ketoprofen-cetyl alcohol melt was poured in 100ml water maintained at room temperature and was stirred continuously

using propeller blade (2500rpm).The Ketoprofen beads obtained after solidification of dispersed droplets were separated by filtration and dried at room temperature.

Yield and drug content[27]
Beads were weighed after drying and percent yield was calculated.
100mg of beads were dissolved in 100ml ethanol by shaking for 30 minutes. The solution was analyzed spectrophotometrically (Shimadzu,Japan) at 260nm after sufficient dilution with phosphate buffer pH 7.4.

Differential scanning calorimetry (DSC)
A DSC study was carried out to detect possible polymorphic transition during the crystallization process. DSC measurements were performed on a DSC DuPont 9900, differential scanning calorimeter with a thermal analyzer.

Fourier transform infrared (FTIR) spectroscopy
The FTIR spectral measurements were taken at ambient temperature using a Shimadzu, Model 8033 (USA). Pure drug, spherical agglomerates and recrystallized samples were dispersed in KBr powder and the pellets were made by applying 5 ton pressure. FTIR spectra were obtained by powder diffuse reflectance on FTIR spectrophotometer.

X-ray analysis
X-Ray powder diffraction patterns were obtained at room temperature using a Philips X' Pert MPD diffractometer, with Cu as anode material and graphite monochromator, operated at a voltage of 40 mA, 45 kV. The samples were analyzed in the 2θangle range of 3-50and the process parameters used were set as scan step size of 0.0170 (2θ), 2θ values were processed using multidimensional minimization programme to calculate cell volume, cell parameters and space grouping.

Scanning electron microscopy (SEM)
Scanning electron microscopic (Joel- LV-5600, USA, with magnification of 250x) photographs were obtained to identify and confirm spherical nature and Surface topography of the crystals.

Micromeritic properties
Particle size of recrystallized samples and pure samples were determined by microscopic method using calibrated ocular micrometer and size of spherical agglomerates was determined by sieving method. Apparent particle densities of agglomerated and unagglomerated crystals were measured using a Pycnometer. Carr's index was determined from powder volumes at the initial stage and after 1250 tappings to constant volume (Electolab, Mumbai). The angle of repose of agglomerated and commercial crystals was measured by fixed funnel method.

In vitro release studie[29]:
The dissolution studies were performed in simulated gastric fluid for 2 hours and replaced simulated gastric fluid with simulated intestinal fluid and dissolution was continued for 8 hours using USP type II dissolution test apparatus (Electrolab, India). Ketoprofen beads equivalent to 300mg drug was placed in the dissolution vessel containing 900ml of dissolution medium maintained at 37±0.5 °C and stirred at 100rpm. Samples were collected periodically and replaced with fresh dissolution medium. Concentration of ketoprofen was determined spectrophotometrically at 260nm and 261nm respectively. Analysis of dissolution data was done by using 'PCP-Disso-v2.08' software, India.

RESULTS AND DISCUSSION

Ketoprofen beads were prepared by Melt solidification technique using cetyl alcohol at different concentrations. This technique involved addition of ketoprofen-cetyl alcohol mass to the aqueous phase at room temperature followed by stirring at 2500rpm. Since ketoprofen has low glass transition temperature Tg (-26°C), it can maintain liquid state after melting for longer period of time during which stirring of ketoprofen-cetyl alcohol melt can done to obtain beads. During this process emulsification and hardening was achieved due to formation of melt-solidified bonds between drug particles.

Beads were weighed after drying, percentage yield was calculated and data are shown in table.2. For determination of drug content, 100mg of beads equivalent to 5mg of Ketoprofen were triturated and dissolved in 100ml of ethanol by shaking for 30min. The solution was analyzed spectrophotometrically at 260nm after sufficient dilution with phosphate buffer pH 7.4 and the results is shown in table 3. The results shows that as the concentration of cetyl alcohol increases, percentage yield of beads decreases. It was observed that Ketoprofen was uniformly distributed in all the formulations.

Table 2: Percentage yield of ketoprofen beads

Formulation code	Quantity of ketoprofen and cetyl alcohol used	Amount of ketoprofen beads obtained (gms)	Percentage yield
F1	5gm	4.35± 0.5	87%
F2	5gm	4.31± 0.2	86.2%
F3	5gm	4.21± 0.6	84.2%
F4	5gm	4.31± 0.3	86%
F5	5gm	4.14± -0.7	82%

Standard Deviation mean n=3

Table 3 - Results of drug content (mg/ 100ml)

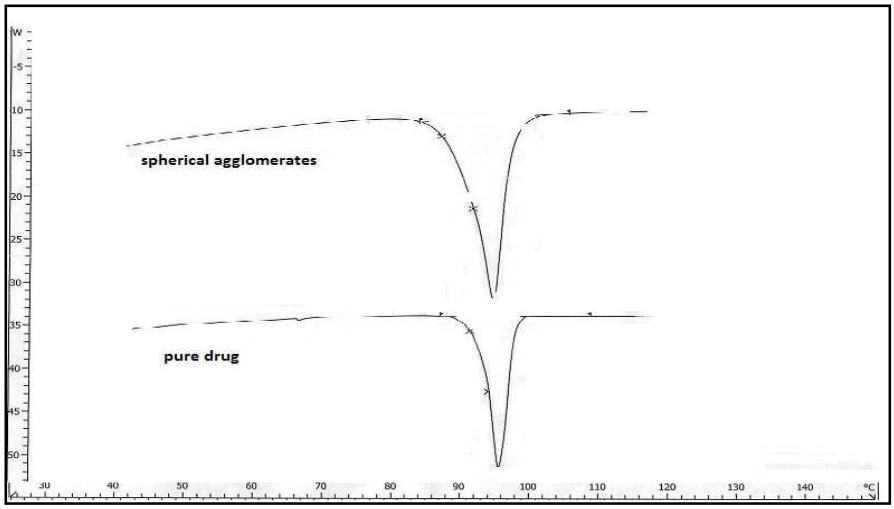
SL.No.	Formulation No.	Drug content (mg/100 ml)				
		Trial I	Trial II	Trial III	Mean ±D*	%DrugContent
1	F1	4.85	4.75	4.92	4.84 ± 0.08	98.4
2	F2	4.96	4.9	4.97	4.94 ± 0.03	98.8
3	F3	4.89	4.94	4.95	4.93 ± 0.03	98.6
4	F4	4.98	4.9	4.84	4.91± 0.07	98.2
5	F5	4.76	4.82	4.88	4.827± 0.04	96.5

Standard Deviation mean n=3

The DSC thermograms (fig. 1) shows a sharp endothermic peak for all the ketoprofen crystals. This one step melt might be due to only one crystal form (Triclinic) of the ketoprofen formed during the crystallization process, thus indicating that ketoprofen did not under go any crystal modification. The temperature range of the endothermic peak of all the ketoprofen crystals lies in

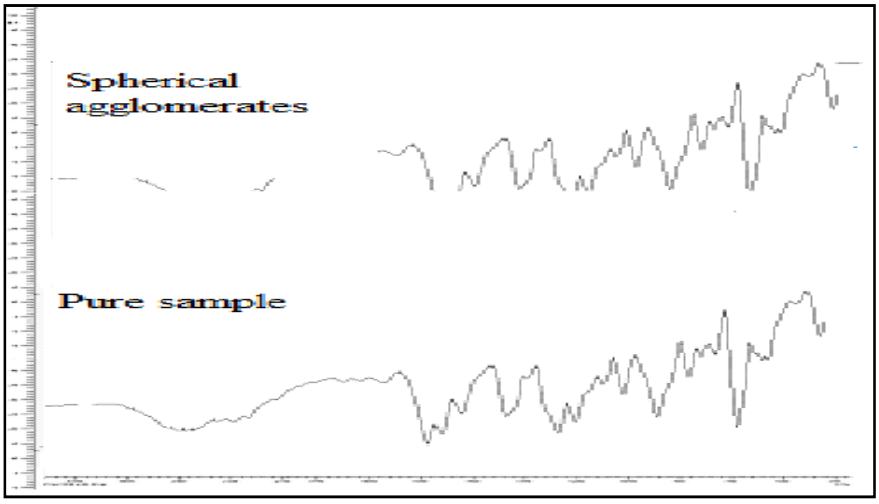
the range of 94^0 to 96^0. Melting points show slight variation as the nature of the crystals might have been affected by the solvent.The melting endotherm for agglomerated ketoprofen was 96.58° with decreased enthalpy of (175.01 J/g) indicating decreased crystallinity.

Fig. 1: DSCthermograms of Ketoprofen



All the crystals have exhibited general characteristic peaks at 2983-2930 cm^{-1} (Aromatic C-H stretch carboxylic acid O-H stretch), 1695-1649 cm^{-1} (C=O stretch), 1595 cm^{-1} (Aromatic C=C stretch), 1437 cm^{-1} (CH-CH_3 deformation), 2891 cm^{-1} ((C-H) stretch plus O-H deformation), 1690 cm^{-1} (Carboxylic O-H out of plane deformation), 860-640 cm^{-1} (C-H out of plane deformation for substituted aromatic) (fig. 2). Specific changes in IR spectra are not very clear, could be due to variations in the resonance structure, rotation of a part of a molecule or certain bonds. Alteration could be due to minor distortion of bond angles, or even a result of the presence of a solvent of crystallization.

Fig. 2: FT-IR spectra of Ketoprofen Samples



All the samples showed similar peak positions (2θ) in X-ray diffraction, formation of different polymorphs of ketoprofen was ruled out. However relative intensities of XRD peaks were modified (fig. 3). This could be attributed to the markedly different crystal habits of the samples (Table 4). Therefore the relative abundance of the planes exposed to the X-ray source would

have been altered, producing the variations in the relative intensities of the peak or may be due to differences in crystal sizes.

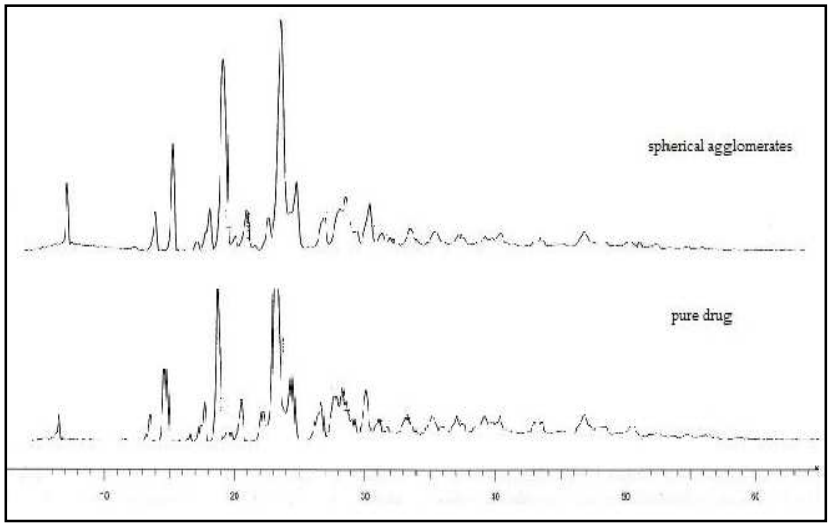
Table 4: different cell parameters obtained for ketoprofen pure sample and beads from xrd data.

	A	B	C	A	B	Γ	Unit cell volume
Pure sample	12.0807	12.213	16.227	94.22	71.76	145.4	1212.19
Ketoprofen beads	6.8634	10.890	14.494	96.27	83.42	54.97	860.67

a, b, c – three sides of cell expressed in A^0.

α, β, γ - three angles of the cell expressed in degrees

Fig. 3:X-ray diffraction spectra of Ketoprofen



Crystals of pure ketoprofen sample are of the smallest size (5-11 µm) and they have irregular shapes. So the resultant agglomerates had a rough surface (fig's. 4-5). Agglomerates obtained were spherical in shape with size 350-830 µm.

Fig. 4 SEM of Ketoprofen pure sample.

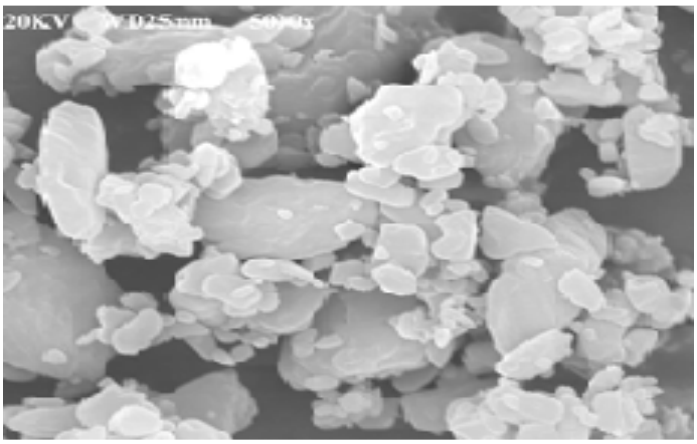
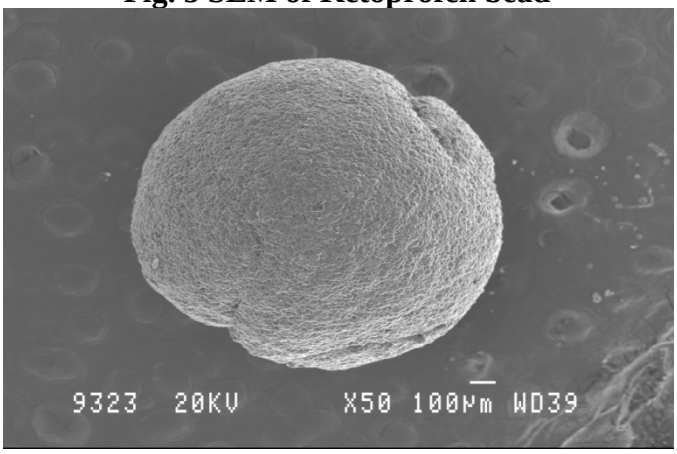


Fig. 5 SEM of Ketoprofen bead



The differences in the bulk densities may be related to their markedly different crystal habits, leading to different contact points, frictional and cohesive forces between the crystals Spherical agglomerates exhibited higher packing ability than pure sample. It is due to lower surface area and wider particle size distribution of spherical agglomerates. The smaller crystals might have settled in voids between larger particles. Three measures of flowability were utilized to analyze the flow of particles. Flow rate measurement allowed quick estimation of flow properties. Angle of repose is able to provide gross measurements of the flowability of crystals. Pure sample exhibited higher angle of repose than spherical agglomerates, due to irregular shape and smaller crystal size. The higher flowability of spherical agglomerates was due to perfect sphericity and larger size of the crystals. The compressibility index is a simple and fast method for estimating flow of powder. Powders with compressibility above 40% had poor flow. Flow rates are in agreement with morphology and bulk density, spherical agglomerates with low bulk density exhibits better flow properties (Table 5).

Table 5: micromeritic properties of ketoprofen pure sample and beads.

Properties	Pure sample	Ketoprofen beads
Particle size (µm)	5-11	350-830
Flow rate (gm/Sec)	No flow	8.37
Angle of repose	41.01	28.07
Tapped density (gm/ml)	0.9302±0.006	0.2159±0.05
Bulk density(gm/ ml)	0.6692±0.0034	0.1892±0.004
Carr's index	28.05	12.37
Porosity (%)	0.3844	0.9086
Friability (%)	-	0.7439±0.32

In-vitrodissolution studies were carried out using simulated gastric fluid and simulated intestinal fluid for pure drug and formulations. The results are shown in table.6-11 and figure.6-12. From the results it was observed that the concentration of cetyl alcohol has affected the percentage release. With increase in cetyl alcohol concentration, the drug diffusion was decreased. This could be due to insoluble nature of cetyl alcohol within which the drug is entrapped. The plots of release kinetics, Higuchi plots demonstrates that the drug release was by diffusion mechanism and follow first order kinetics.

Table 6: Dissolution of pure drug (Ketoprofen) in simulated gastric fluid

Pure drug	**Percentage drug release in time (hours) Mean ±S.D**	
	1	**2**
Ketoprofen	0.8±0.56	1.01±1.35

Standard deviation n=3

Table 7: Dissolution of pure drug (Ketoprofen) in simulated intestinal fluid

Pure drug	**Percentage drug release in time (hours) Mean ± S.D**		
	1	**2**	**3**
Ketoprofen	42.56±0.28	76.09±1.83	98.96±0.83

Standard deviation n=3

Table 8: Dissolution of Ketoprofen beads formulations F1-F5 in simulated gastric fluid from 1- 2 hours.

Formulation No.	**Percentage drug release in time (hours) Mean ±S.D**	
	1	**2**
F1	1.59±0.8	1.78±1.3
F2	1.47±0.1	1.69±0.5
F3	1.39±0.9	1.63±1.2
F4	1.26±1.1	1.49±1.2
F5	1.07±0.5	1.31±1.6

Standard deviation n=3

Table 9: Dissolution of Ketoprofen beads formulations F1-F5 in simulated intestinal fluid from 3-10 hours.

Forl. no.	Percentage drug release in time (hours) Mean ± S.D							
	3	4	5	6	7	8	9	10
F1	43.63±0.6	64.59±0.4	70.49±0.2	74.29±2.5	78.90±08	82.00±1.4	87.44±2.5	96.22±0.1
F2	35.88±0.9	42.07±0.3	53.35±2.1	66.35±1.6	73.00±1.4	79.58±3.6	86.02±2.3	90.66±2.1
F3	24.52±0.4	26.85±1.2	36.01±0.9	47.19±3.2	61.16±2.4	71.42±0.8	78.87±1.7	86.02±1.8
F4	5.21± 1.3	30.04±0.9	44.36±2.6	49.50±3.6	53.57±2.2	72.72±1.7	76.68±2.5	81.98±1.9
F5	19.67±0.9	21.26±0.7	28.34±2.8	35.06±0.9	39.57±3.6	45.57±1.4	53.67±2.3	64.00±1.6

Standard deviation n=3

Table 10: Release kinetics of Ketoprofen beads formulations F1-F5 in simulated gastric fluid

Time In Hours	Formulation No									
	F1		F2		F3		F4		F5	
	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log%C.R
1	98.41	1.993	98.53	1.993	98.61	1.994	98.74	1.994	98.93	1.995
2	98.22	1.992	98.31	1.992	98.37	1.992	98.51	1.993	98.69	1.994

Table 11: Release kinetics of Ketoprofen beads formulations F1-F5 in simulated intestinal fluid

Time In Hours	Formulation No									
	F1		F2		F3		F4		F5	
	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log%C.R	%C.R	Log% C.R
3	56.37	1.75	64.12	1.81	75.48	1.88	74.79	1.87	80.33	1.90
4	35.41	1.55	57.93	1.76	73.15	1.86	69.96	1.84	78.74	1.89
5	29.51	1.47	46.65	1.67	63.99	1.80	55.64	1.74	71.66	1.85
6	25.71	1.41	33.65	1.53	52.81	1.72	50.5	1.70	64.94	1.81
7	21.1	1.32	27	1.43	38.84	1.59	46.43	1.66	60.43	1.78
8	18	1.25	20.42	1.31	28.58	1.46	27.28	1.43	54.43	1.73
9	12.56	1.1	13.98	1.14	21.13	1.32	23.32	1.36	46.33	1.66
10	3.78	0.58	9.34	0.97	13.98	1.14	18.02	1.25	36	1.55

C.R – Cumulative retained

Figure 6: Dissolution graph of pure drug (Ketoprofen) in simulated Gastric fluid.

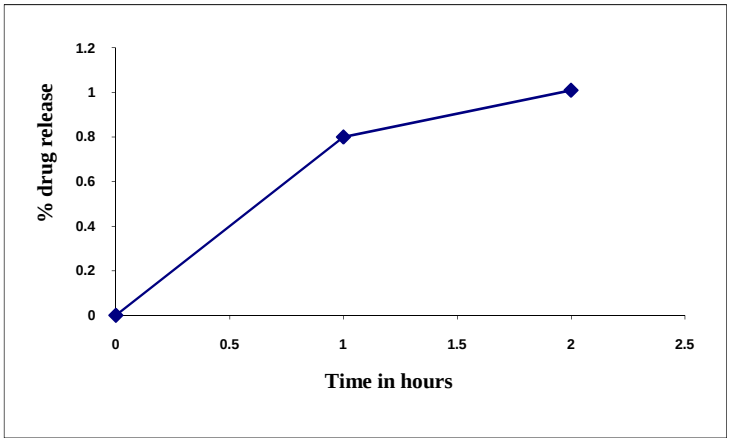


Figure 7: Dissolution profile of pure drug (Ketoprofen) in simulated intestinal fluid

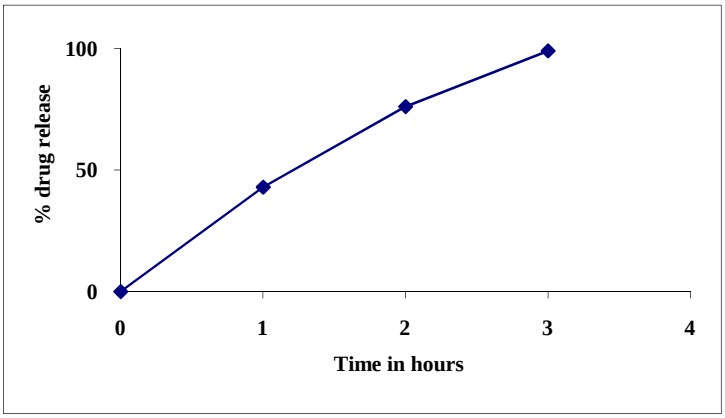


Figure.8 Dissolution graph of Ketoprofen beads in simulated gastric and intestinal fluid.

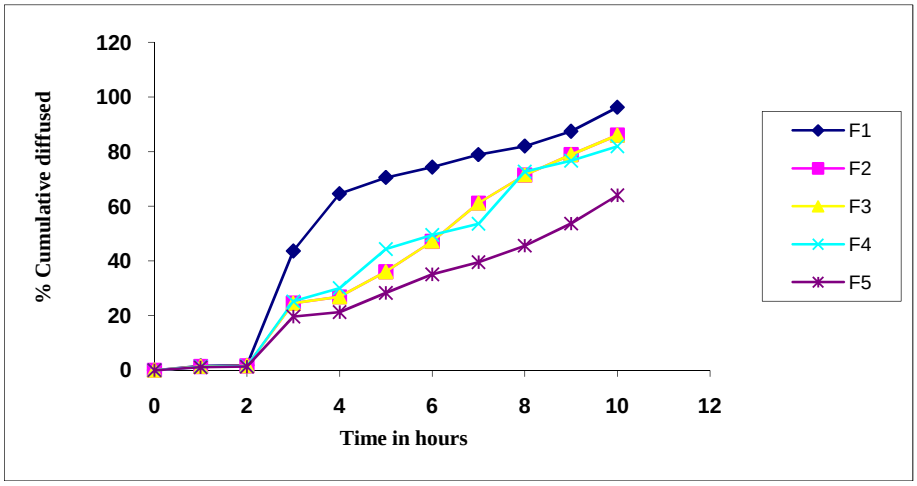


Figure 9: Release kinetics of formulations F1-F5 in simulated gastric fluid

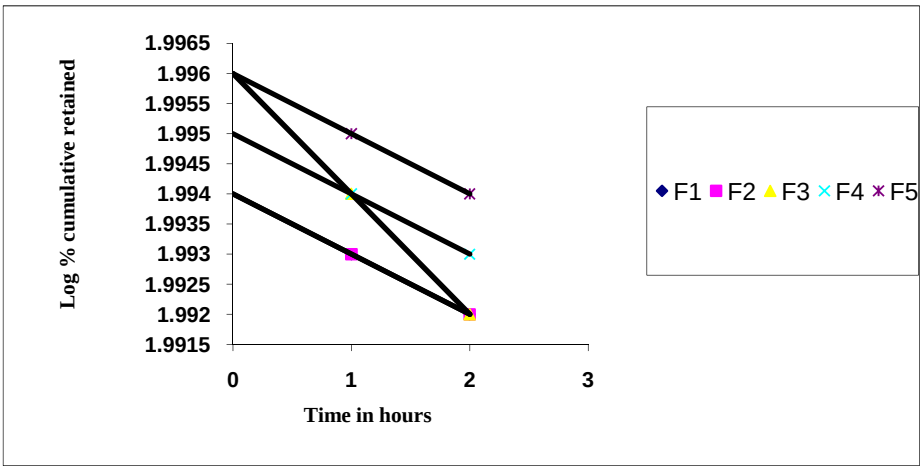


Figure 10. Higuchi plots of formulations F1-F5 in simulated gastric fluid

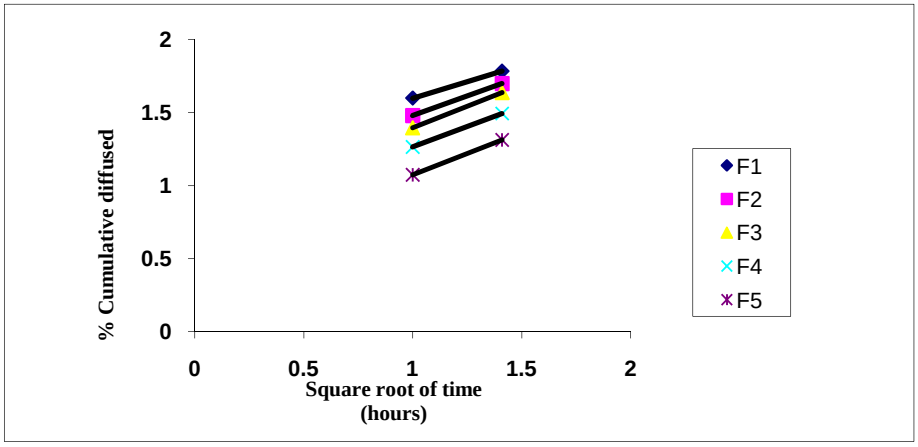


Figure11: Release kinetics of formulations F1-F5 in simulated intestinal fluid

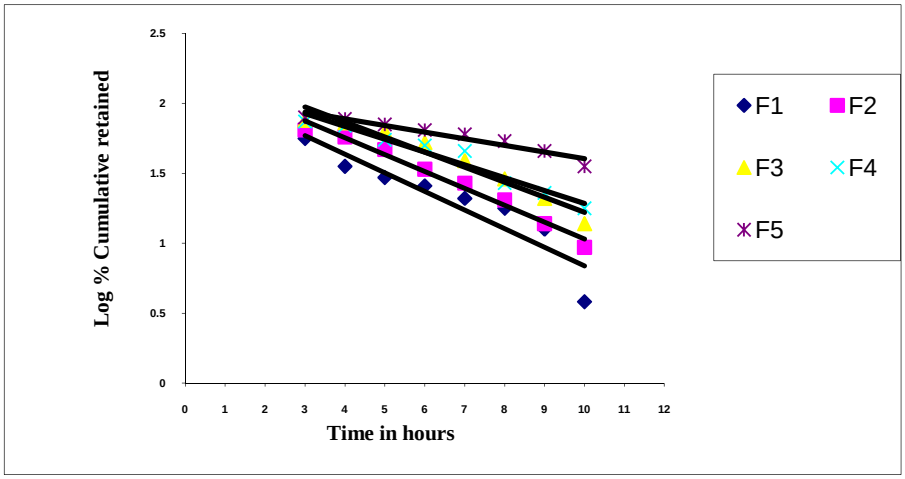
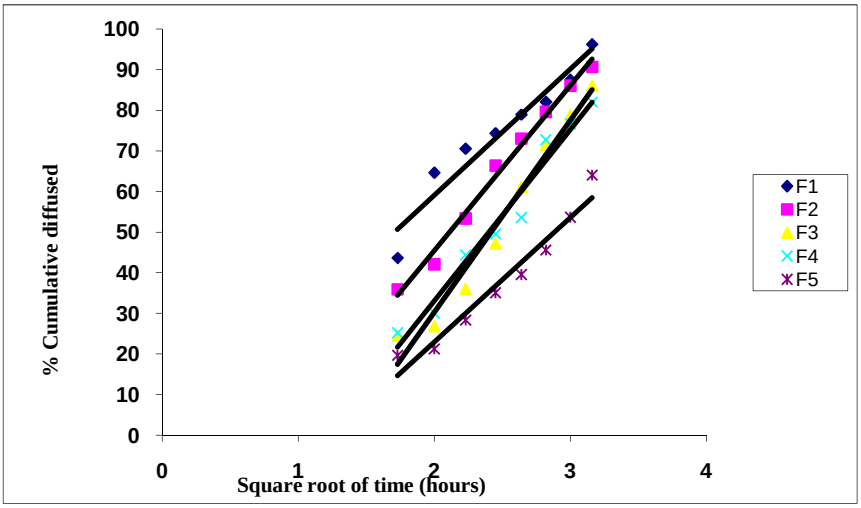


Figure 12. Higuchi plots of formulations F1-F5 in simulated intestinal fluid



CONCLUTION

Ketoprofen beads were prepared by melt solidification using cetyl alcohol as an excipient. The prepared beads were evaluated for physicochemical properties such as percent yield, drug content, compatibility of drug with excipient by FT-IR spectroscopy, scanning electron microscopy, micromeritic properties, drug release characteristics, x-ray diffraction. Ketoprofen is a potential candidate for the preparation of beads by melt solidification technique. The beads obtained were spherical in shape. Formulation F1 has showed highest yield (87%), The drug was uniformly distributed in all the formulations. Drug was found to be compatible with the excipient used. The beads exhibited good flow properties. Formulation 1 has showed highest drug release96.22% at 10th hour. The mechanism of drug release was by diffusion and following 1st order kinetics. X-ray powder diffractograms of drug and beads have shown no significant difference in the inter planar distance (d) values. Hence there are no polymorphic changes. Hence it is concluded that Ketoprofen could be formulated into beads as sustained drug release dosage form by melt solidification technique.

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REFERENCES

[1] The Merck index 10th edition. Page no 1251. Publisher: Merck and Co. Inc. **1983**.
[2] Cristopher haslett, Principles and practice of medicine, 19th edition, page no:990, publisher: Churchill livinstone.
[3] Paradkar.A, Maheshwari.M, Tyagi.A.K, Chauhan.B, Kadam.S.S, *AAPS Pharm SciTech* **2003**; 4 (4).
[4] Anant.R.Paradkar, Manish Maheshwari, Anant.R.Ketkar, Bhaskar chouhan, *International journal of pharmaceutics* 255 (**2003**) 33-42.
[5] Manish maheshwari, Anant R.Ketkar, Bhaskar chauhan, Vinay B.Patil, Anath R.Paradkar. *International journal of pharmaceutics* 261 (**2003**) 57-67.

[6] Reynolds, J.E.F.Eds. In; Martindale. The extra pharmacopoeia, 28th edition, The pharmaceutical press, London, **1982**.
[7] B.Campisi, D.Vojnovic, D.Chicco, R.Phan-Tan-Luu. *Chemometrics and intelligent laboratory systems.* **1999**, 48,59-70.
[8] Jung-Woo Kim, Joachim Ulrich. *International Journal of Pharmaceutics* 257 (**2003**), 205-215.
[9] Indian Pharmacopoeia, The controller of publications, Delhi, **1996**, IIA
[10] Ainley Wade and Paul J Weller. Hand book of pharmaceutical excipients 2nd edition, page no. 99.Publisher: The Pharmaceutical Press, London, **1994**.
[11] N.Tarimci et.al *Journal of the pharmaceutical society of Japan*. 121 Mar. P.239-245, **2001**
[12] Yamada.T et al, *Journal of controlled release*, 75 (3) p 271-282, **2001**
[13] N.Tarimci et.al. *International journal of pharmaceutics*. 147 Feb 14 p 71-77, **1997**
[14] G.F.Palmieriet.al. *Drug development and industrial pharmacy*. 22 (9-10) : p 951-957, **1996**
[15] The pharmaceutical codex – principles and practice of pharmaceutics12th edition page no.933-935.
[16] U.S.Pharmacopoeia 23/National formulary 19, Asian edition, **2000**.
[17] Alfred martin, Physical pharmacy, 4th edition page no. 423, Publisher: LEA and Febriger **1993**
[18] Analytical profiles of drug substances, volume 10, edited by Klaus Florey. Page no. 443, Publisher: Academic Press, **1981**
[19] British pharmacopoeia, Her Majesty's stationary office, London **1998**,I.
[20] Novel drug delivery systems 2nd edition Yie W.Chien page no. 43 Publisher: Marcel Decker, Inc. **1992**.
[21] Controlled drug delivery, concepts and advances S.P.Vyas, Roop K.Khar, page no. 202, Publisher: Vallabh Prakashan 1st Edition, **2002**.
[22] Michael E.Aulton, Pharmaceutics: The science of dosage form design. Page no.204, Publisher: Churchill Livingstone, 1st edition, **1988**.
[23] S.R.Vaithiyalingam, P.Tulian, W.Wilber, I.K.Reddy. *Drug.Dev.Ind.Pharm*. Volume 28, Number 10, **2002**. 1231
[24] Nicholas.G, Losdi, Sustained release dosage forms, Leon Lachmann; Herbert.A. Lieberman and Lachmann.Theory and practice of industrial pharmacy. **1991**. Page no: 430 - 456. Publisher: Marcel Decker, Inc
[25] N.K.Jain, B.K.Patil, *Eastern Pharmacist*, Sep. **1993**, Page no: 35 - 42. Publisher: Pamposh Publications.
[26] Y.E.Zhang and J.BSchwartz. *Drug Development and Industrial Pharmacy*. Volume-29, Number 2, **2003**, Publisher: Marcel Decker, Inc.
[27] D.M.Brahmankar and Sunil B.Jaiswal.Biopharmaceutics and Pharmacokinetics Atreatise. Publisher: M.K.Jain, Vallabh Prakashan 1st edition **1995**.
[28] Instrumental methods of analysis. M.chatwal, Bharath publications. Page no. 264, 4th edition, **1998**.
[29] P.L.Madan.Biopharmaceutics and Pharmacokinetics Publisher: Jay pee Brothers Medical publisher (p) Ltd, 1st edition, **2002**